REMARKS

Claims 59, 68-75 and 77-78 are pending.

The claims were amended by removing the phrase "specific antibody" and steps (iii) and (iv) of the claimed method. No language was added to the claims. The applicants respectfully submit that no new matter has been added. It is believed that this Amendment is fully responsive to the Office Action dated **July 27, 2005**.

New claim 78 is objected to because it refers to using a "pectin" as a specific binding agent for differentiating between two different types of thyroglobulin. (Office Action p.2)

The Examiner noted that the word "pectin" should be corrected to read lectin. The amendment has been made as the Examiner suggested.

Claims 59 and 68-78 are/remain rejected under 35 USC §112, first paragraph, as failing to comply with the written description requirement for the reason of record. (Office Action p.3)

The Office Action indicated that the basis for this rejection is that the claimed methods are not described to the extent that the claimed methods read on methods comprising the use of "specific antibodies capable of binding to a specific structure of a sugar chain of a first type of thyroglobulin."

In response to this rejection, all references to a "specific antibody" have been deleted from all pending claims making this rejection now moot.

Claims 59, 68, 69, and 74 are rejected under 35 USC §103(a) as being unpatentable over either Nakamura (U.S. Patent No. 5,571,729; issued 11/5/1996) or Satomura (U.S. Patent No. 5,780,247; issued 7/14/1998; effective filing 1/5/1991) in view of either Yamamoto (of record), Tarutani (of record), Survilo (Survilo, L.I. et al., Vestsi Akademii Navuk Belarusi, Seryya Khimichnykh Navuk, 4: 103-107, 1997; abstract only), or Stanta (Stanta, G. et al., Thyroidology, 3(1): 7-12, 1991). (Office Action p.5)

The issue is whether in the combination of the cited references is there any disclosure or suggestion for a method which takes a sample and *measures* conjugated Tg, non-conjugated Tg and total Tg and *compares* the ratio of either conjugated or non-conjugated Tg to total Tg with the same ratio for both a known normal sample and a known benign sample and *determines the malignancy of a thyroid tumor* based on a comparison of the ratios with the normal ratio *and* the benign ratio.

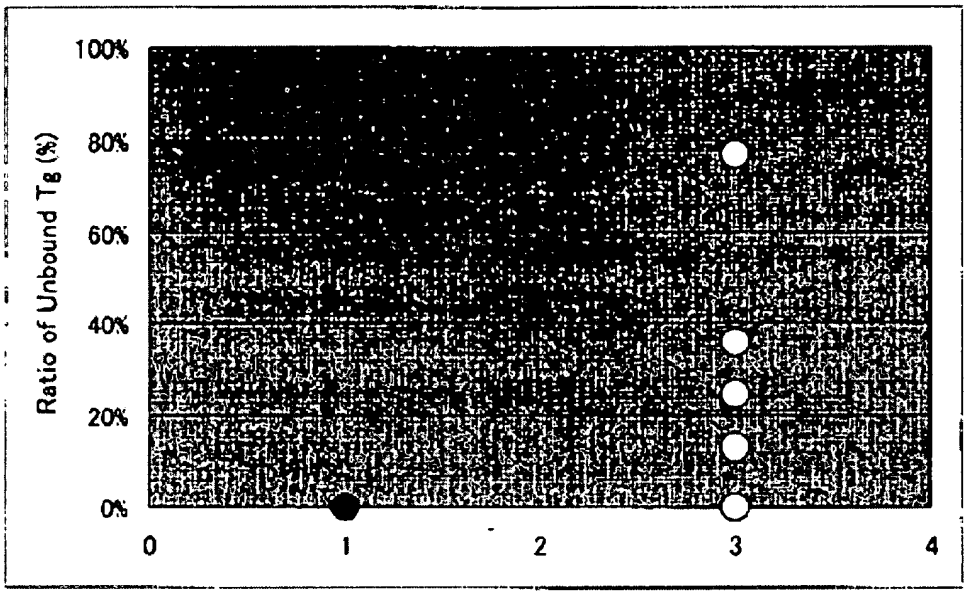
Simply put, measurements standing alone are not determinations tumor malignancy much less anything more than measurements standing alone. As will be shown below, the conclusion that measurements disclosed in various references equals a method for making a malignancy determination is not logical, because this reasoning would foreclose all determinations by obviousness and would suggest for future patent applications that raw data is by itself conclusory.

The Office Action admits at the bottom of p.6 and top of p.7 that neither Nakamura nor Satomura teaches method directed to measuring different types of Tg based on their reactivity to lectins, and neither Nakamura nor Satomura teaches a relationship between different Tg lectin-reactivity with malignancy of a thyroid tumor.

The Office Action mentions that in Yamamoto ConA affinity chromatography makes a demonstration about Tg from *malignant* thyroids and Tg from *normal* thyroids. Further in Yamamoto, RCA affinity chromatography makes a demonstration about Tg from *malignant* thyroids and Tg from *normal* thyroids. The conclusion on p.8 of the Office Action that the ConA reactivity or RCA-reactivity may be used to distinguish Tg from malignant from Tg derived from *benign* or normal thyroids does not logically follow from the showing in Yamamoto, as explained, nor is there any suggestion at all to measure normal and benign and compare with normal and benign followed by making a determination based on the comparison. The combination is missing the key steps in the process as now claimed.

As for Tarutani, the applicants have showed the Table II of Tarutani by the following graph (Tarutani-Figure, Ratio of Unbound Tg (%)) for the purpose of showing that among other problems, Tarutani is empirically not conclusive if interpreted to try to suggest the claimed invention.

<Tarutani-Figure>



1 = normal
2 = benign
3 = malignant

As is clear from the above graph of Table II of Tarutani, the ratio from benign and the ratio from malignant are completely overlapped. The relationship between the ratio from malignant and the ratio from benign cannot be known from the result. The result shows ***malignant cannot be distinguished from benign*** by comparing the ratio obtained by Tarutani. Therefore, the skilled artisan cannot know that the malignancy can be determined by using the ratio from the disclosure of Tarutani.

On the other hand, as is clear from the figures of present invention, the ***present invention can distinguish not only malignant from normal, but also malignant from benign.***

Indeed, in Fig.1 of the present invention, when the ratio from sample is higher than that from normal standard and higher than that from benign standard, ***the sample can be determined as malignant but not normal, and not benign.*** That is, malignant can be distinguished from benign and normal by the method as now claimed. Tarutani does not disclose this method for determining malignancy (whether the sample is malignant or benign).

Technically, the physical measurement method of Tarutani is also different. Tarutani measures the amount of the soluble protein in the sample but does not measure the direct amount of thyroglobulin specifically. The thus obtained soluble protein amount may contain thyroglobulin and other water-soluble proteins. On the other hand, the present invention measures an amount of Tg specifically by using lectins.

As a result, the claimed invention can distinguish not only malignant from normal but also malignant from benign, though the relationship between the ratio from malignant and the ratio from benign cannot be known from Tarutani.

As for Survilo, the abstract states "Tg samples from cancerous thyroids did not bind as strongly to ConA-Sepharose as did those from normal or goitrous thyroids indicating that they have a different ***carbohydrate*** compn." This disclosure is combination fails to suggest the claimed invention because first it only discloses measurements and second there is no mention as to the

relationship of Tg binding between normal and goitrous. The only comparison was made with cancerous thyroids, which completely lacks the steps necessary for the claimed intention.

As for Stanta, the Office Action mentions that Stanta discloses Tg from a *normal* thyroid gland and from a well differentiated *carcinoma thyroid.* Again this reference simply adds to the literature about using a normal and a carcinoma thyroid. The reference does not mention the application of Tg to a normal, *benign* and a carcinoma thyroid, therefore it does not rebut our previous arguments.

The Office Action states on p.10 of the Office Action that our previous arguments are not persuasive because Yamamoto, Tarutani, Survilo and newly cited Stanta, demonstrate a differential lectin-binding pattern between malignant and non-malignant thyroids. Again, Stanta does not at all disclose Tg from a normal, benign ***and*** malignant thyroid, it is merely cumulative to the previously cited references.

Based on the showing above, it is respectfully requested that rejection be reconsidered and overcome.

Claims 70, 71 and 78 are rejected under 35 USC §103(a) as being unpatentable over Katoh (U.S. Patent No. 5,591,589; issued 1/7/1997) in view of either Yamamoto (of record), Tarutani (of record), Survilo (Survilo, L.I. et al., Vestsi Akademii Navuk Belarusi, Seryya Khimichnykh Navuk, 4: 103-107, 1997; abstract only), or Stanta (Stanta, G. et al.,

Thyroidology, 3(1): 7-12, 1991). (Office Action p.11)

The Office Action admits on p.12, text lines 7-9 that Katoh fails to teach methods directed to measuring different types of Tg based on their differential reactivity to lectins and Katoh fails to teach a relationship between differential Tg lectin-reactivity with malignancy to a thyroid tumor.

The applicant's position is that without more, the combination of Katoh with previously mentioned references cannot logically lead the skilled artisan to the claimed invention. Again, on p.13 of the Office Action, the conclusion is made that the claimed invention is obvious in light of ConA-reactivity and the RCA-reactivity shown in Yamamoto combined with Katoh.

However, nowhere in either reference is there a suggestion to make a determination based on a comparison with both a benign sample and a normal sample. It is not enough to show that Tg may bind differently from malignant thyroids and normal thyroids, there must be a suggestion that one makes a ***double comparison*** before making a determination about the malignancy of an unknown sample. Without such suggestion, the disclosure of measurements do not spontaneously organize themselves into methods for determining diseases.

Because Katoh does not supply the disclosure necessary to make a logical conclusion of obviousness, its combination with Tarutani, Survilo and Stanta also fail for the same reasons mentioned in the previous rejection.

It is respectfully requested that this rejection be reconsidered.

Claim 73 remains rejected under 35 USC §103(a) as being unpatentable over Canfield (WO/87/00289;) in view of Yamamoto (of record). (Office Action p.16)

The rejection admits on p.17, text lines 6-7 that Canfield fails to teach that measuring levels of desialated Tg is correlated to thyroid malignancy.

Just because Canfield teaches a way to distinguish desialated Tg from normally glycosylated Tg, this in combination with Yamamoto does not suggest measuring the normal, benign and the unknown sample and comparing with unknown sample with **both** the previously measured normal and benign samples. In other words, there has yet to be suggested that the *purpose* of measuring the normal **and** benign is to compare with an unknown sample. Instead the combination of references disclose uncoordinated measurements and the rejection concludes that they are "obviously" related in the same manner as the claimed method. Simply put, the suggestion of the claimed method is completely devoid in the references.

Claim 75 remains rejected under 35 USC §103(a) as being unpatentable over Katoh (supra) in view of Canfield (WO/87/00289;) and further in view of Yamamoto (supra) for the reasons of record. (Office Action p.18)

The mere addition of Katoh, to the combination of Canfield and Yamamoto also fails because the suggestion of the claimed method is completely devoid in the references. Measurements by themselves are not conclusions or disease determinations but still only measurements. There is not a sentence in any of the references which suggests making a disease determination based on a

comparison with a normal measurement and a benign measurement. Therefore logically, the rejection fails because a key step in the claimed method is missing and nowhere suggested.

Claims 59, 68, 69, and 74 remain rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1, and 5-9 of US Patent No. 5,780,247 in view of either Yamamoto (of record), Tarutani (of record) or Survilo (Survilo, L.I. et al., Vestsi Akademii Navuk Belarusi, Seryya Khimichnykh Navuk, 4: 103-107, 1997; abstract only). (Office Action p.22)

The applicants acknowledge this double patenting rejection and assert that a terminal disclaimer can be filed to overcome the rejection when the other claims are found allowable.

Claims 70, 71, and 78 remain rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1, and 3 of US Patent No. 5,591,589 in view of either Yamamoto (of record), Tarutani (of record) or Survilo (Survilo, L.I. et al., Vestsi Akademii Navuk Belarusi, Seryya Khimichnykh Navuk, 4: 103-107, 1997; abstract only). (Office Action p.23)

The applicants acknowledge this double patenting rejection and assert that a terminal disclaimer can be filed to overcome the rejection when the other claims are found allowable.

In view of the aforementioned amendments and accompanying remarks, the claims, as

amended, are in condition for allowance, which action, at an early date, is requested.

If, for any reason, it is felt that this application is not now in condition for allowance, the Examiner is requested to contact the applicants undersigned attorney at the telephone number indicated below to arrange for an interview to expedite the disposition of this case.

In the event that this paper is not timely filed, the applicants respectfully petition for an appropriate extension of time. Please charge any fees for such an extension of time and any other fees which may be due with respect to this paper, to Deposit Account No. 01-2340.

Respectfully submitted,

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